Unexpected reaction course of 3-Amino-5-aryl-1H-pyrazoles with Dialkyl Dicyanofumarates

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Abstract: On treatment of 3-amino-5-aryl-1H-pyrazoles 1 with dialkyl dicyanofumarates (=(E)-but-2-enedioates) 4 in boiling 1,2-dichloroethane, two competitive reactions occurred leading to 3-aryl-5-cyano-6,7-dihydro-6-oxo-1H-pyrazolo[3,4-b]pyridine-4-carboxylates 10 and 7-amino-2-arylpyrazolo[1,5-a]pyrimidine-5,6-dicarboxylates 11. In DMF at room temperature, as well as at 100°, only compounds 10 were isolated. The formation of the major products of type 10 was rationalized via Michael addition of 1 as a C(4)-nucleophile onto 4, followed by HCN elimination and lactamization. On the other hand, the minor products 11 result from a Michael addition of 1 onto 4 via the NH2 group, and subsequent HCN elimination and cyclization. The structures of the products have been established by X-ray crystallography.

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Unexpected Reaction Course of 3-Amino-5-arylpyrazoles with Dialkyl Dicyanofumarates

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On treatment of 3-amino-5-aryl-1*H*-pyrazoles **1** with dialkyl dicyanofumarates **4** in boiling 1,2-dichloroethane, two competitive reactions occurred leading to 5-aryl-3-cyano-2,7-dihydro-2-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates **10** and 4-amino-7-arylpyrazolo[2,3-*a*]pyrimidine-2,3-dicarboxylates **11**. In DMF at room temperature as well as at 100°, only compounds **10** were obtained. The formation of the major products of type **10** was explained *via Michael* addition of **1** as a C(4) nucleophile onto **4**, followed by HCN elimination and lactamization. On the other hand, the minor products **11** result from a *Michael* addition of **1** onto **4** *via* the NH_2 group and subsequent HCN elimination and cyclization. The structures of the products have been established by X-ray crystallography.

1. Introduction. – The importance of 3-amino-5-arylpyrazoles **1** as valuable building blocks for the synthesis of various fused heterocycles is well documented in original articles [1] as well as in patents [2]. In addition, modifications of the structure at the NH_2 group were performed in many instances to obtain biologically active products [1c][3]. In some cases, aminopyrazoles **1** were used as *Michael* donors in reactions with substrates such as tetracyanoethene (TCNE) [1h] or benzylidenemalononitrile derivative [1e]. In both cases, the reaction was initiated by the attack of the NH_2-group onto the electron deficient C=C bond, and an analogous addition/elimination/cyclization mechanism led to pyrazole[2,3-*a*]pyrimidine derivatives **2** and **3**, respectively (*Scheme 1*).

Scheme 1

In a series of recent publications we reported on reactions of electron-deficient dialkyl dicyanofumarates **4** with amines [4], diamines [5], and ^{2}-amino alcohols [6]. Whereas, in the case of primary and secondary amines, enamines were formed as (*Z*)- and (*E*)-isomers, respectively, *via* an addition/elimination sequence, the reactions with 1,2-diamines yielded cyclic products after subsequent lactamization of the intermediate amino ester. For example, (*S*)-prolinamine (**5**) reacted smoothly with **4a** (R = Me) to give the bicyclic product **6** [5] (*Scheme 2*). Heating of *β*-amino alcohols with **4a** led to morpholin-2-one derivatives **7**. In this case, the stepwise reaction terminated by lactonization [6].

Scheme 2

Finally, reactions of **4** with 3-phenyl-1-azabicyclo[1.1.0]butane (**8**) occurred at room temperature yielding a 3:1 mixture of *cis*- and *trans*-1-azabicyclo[1.1.1]pentane-2,3-dicarboxylates **9** [7].

The goal of the present study was to examine the reaction of **4** with selected 3-amino-5-arylpyrazoles **1** as reaction partners possessing four potential nucleophilic centers. Previously, the structures of **1** were studied by means of different techniques and tautomeric equilibria of **1** both in solution and in the solid state have been discussed [8]. The presence of different tautomeric forms of **1** in solution may result in their ambivalent reactivity towards electrophilic reagents such as *Michael* acceptors.

2. Results and Discussion. – Reactions of equimolar amounts of **1** and **4** were carried out in boiling 1,2-dichloroethane (method *A*), in dimethylformamide (DMF) at room temperature (method *B*), or in DMF at 100° (method *C*). Using method *A*, the progress of the reaction was monitored by TLC, which showed that the conversion of the starting materials was complete after 2 h. The ^{1}H-NMR control of the crude mixture obtained after evaporation of the solvent evidenced the presence of two products containing one and two ester groups, respectively. In all cases, the monoester was the major component, which could easily be separated by trituration of the mixture with MeOH or acetone and subsequent filtration of the precipitate. The minor products obtained from the reactions of **4** with 3-amino-5-(4-methylphenyl)pyrazole (**1a**), containing two ester groups (^{1}H-NMR), were isolated after chromatographic separation (PLC) of the mother liquors obtained after filtration of the major component. Alternatively, when DMF was employed using methods *B* or *C*, the obtained mixtures were diluted with H_2O, and the products precipitated thereby were filtered and found to

be identical with the major component of the reaction performed in 1,2-dichloroethane solution (method *A*).

The structure of the major product **10a** obtained in the experiment with **1a** and **4a** (R = Me) in boiling 1,2-dichloroethane solution (method *A*) was proposed on the basis of the spectroscopic data. The ^{1}H-NMR spectrum ((D$_6$)DMSO) revealed the presence of only one MeO group, but no signal of H-C(4) of the pyrazole ring was observed. In the ^{13}C-NMR spectrum ((D$_6$)DMSO), signals characteristic for MeO (53.3 ppm), CN (115.0 ppm), and two C=O groups (160.2, 163.7 ppm) were registered. All signals for the other sp^2-C atoms appeared between 100 and 150 ppm with low intensities and broadening. The presence of the CaN group as well as an ester and an amide C=O group was confirmed by strong IR-absorption bands (KBr) located at 2229, 1740, and 1659 cm^{-1}. The molecular mass *m/z* 308 corresponded to the formula $C_{16}H_{12}N_4O_3$, which corresponds with a product formed after elimination of HCN and MeOH.

For the elucidation of the structure of the isolated products, different reaction pathways presented in *Scheme 3* can be postulated. As mentioned in the introduction, 3-aminopyrazoles **1** are expected to react as multivalent reagents. Based on the published reactions [1e][1h], one could expect a nucleophilic addition of the NH_2 group of **1** to **4**, followed by elimination of HCN to give the 'enamine-type' product **A**. This intermediate could undergo cyclizations with one of the ester groups leading, after elimination of MeOH, to the six-membered rings **B** or **C** *via C*- or *N*-nucleophilic attack, respectively. Structure **C** can be eliminated, as the collected data do not confirm the presence of a pyrazole H-C fragment. In contrast to **C**, structure **B** can be considered as a likely product of the reaction. On the other hand, an alternative reaction pathway

via C-nucleophilic addition of **1** to **4** would lead to intermediate **D**, which subsequently could undergo lactamization to give the pyrazolo[3,4-*b*]pyridine-2-one derivative **10**.

Scheme 3

Table 1. *Reactions of* **1** *with Dialkyl Dicyanofumarates* **4**

a) Method *A*: Boiling $ClCH_2CH_2Cl$, 2 h; method *B*: DMF, r.t., 16 h; method *C*: DMF, 100°, 11 h

The spectroscopic data presented above did not allow structures **B** and **10** to be distinguished. For this reason, X-ray crystal-structure determinations of the analogous products **10d** and **10k**, obtained from the reactions of **1b** and **1d**, respectively, with **4a**, were performed and proved the structures **10d** and **10k** unambiguously (*Fig. 1*). It has to be mentioned that the two structures in the crystals represent two different tautomers, as in **10d** the H-atom is located on N(7) whereas it is on N(6) in **10k**.

a) b)

Fig. 1. *ORTEP-Plots* [9] *of the molecular structures of* a) **10d** *and* b) *one of the disordered conformations of* **10k** (CF_3 disorder; 50% probability ellipsoids; arbitrary numbering of the atoms)

Analogous compounds of type **10** were obtained as major products of the reactions of **1a**–**1d** with **4a**–**4c** (*Table 1*, methods *A*–*C*). In the reactions of **1a** with **4a**–**4c**, the mother liquors obtained after filtration of the major products **10a**–**10c** were

worked up by preparative TLC, and the minor products **11** were isolated as less polar materials[1]). In all cases, the NMR spectra indicated the presence of two ester groups and H–C(4) of the pyrazole ring. Furthermore, strong IR absorptions at *ca*. 1750 and 1685 cm^{-1} correspond well with those observed for enamines obtained from reactions of **4** with primary amines [4]. In addition, in the case of **11a**, a strong absorption at 3115 cm^{-1} could be attributed to a NH_2 group. As a matter of fact, the absence of the absorption signal of the CN group in the ^{13}C-NMR spectrum of this product suggested that CN present in the intermediate **A** was converted by heterocyclization into the C–NH_2 function. These data suggested that this product was formed *via* the competitive reaction of the NH_2 group of **1** with **4** (*Scheme 3*). In analogy to the described reaction pathway with TCNE [1h], this initial step led to the formation of intermediate **A**, which subsequently underwent heterocyclization by nucleophilic attack of the pyrazole N-atom onto the CN group resulting in the formation of a pyrazolo[2,3-*a*]pyrimidine derivative of type **11**. Apparently, in the intermediate **A**, the two ester groups are *cis*-oriented (*E*-configuration), because this orientation is necessary for the cyclization to give **11**. Finally, an X-ray crystal-structure determination was carried out in the case of **11c**, which proved the structure of the pyrazolo[2,3-*a*]pyrimidine (*Scheme* 3, *Fig. 2*).

Fig. 2. *ORTEP-Plot* [9] *of the molecular structure of* **11c** (50% probability ellipsoids; arbitrary numbering of the atoms)

[1]) The ratio of products **10a** and **11a** did not change when heating of the reaction mixture was extended to 5 h. In an additional experiment, a sample of **11a** was heated in boiling dichloroethane in the presence of a catalytic amount of *p*-TsOH. Even after 3 h, unchanged starting material was recovered quantitatively.

3. Conclusions. – In contrast to typical aliphatic and aromatic primary amines, 3-amino-5-arylpyrazoles **1** react as ambivalent reagents with dicyanofumarates **4**, preferentially as *C*-nucleophiles, and the formed intermediates of type **D** smoothly undergo lactamization to yield pyrazolo[3,4-*b*]pyridin-2-ones **10** in a selective manner. The competitive *Michael* addition of the NH_2 group of **1** onto **4** and subsequent heterocylization *via N*-nucleophilic attack onto the CN group results in the formation of **11**. Whereas reactions of **1** *via* the NH_2 group are common, the reaction initiated by the predominant *C*-nucleophilic attack is observed rarely [10]. It is especially worth mentioning that the reactions of **1** with **4** occur differently than the reported reactions with tetracyanoethene, in which the only reported products are formed *via* initial *N*-nucleophilic attack exclusively [1h].

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Experimental Part

1. *General*. M.p.: *MEL-TEMP. II* (*Aldrich*); uncorrected. IR Spectra: *NEXUS FT-IR* instrument; in KBr or as film; absorptions in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR Spectra: *BRUKER AVANCE III* instrument (^{1}H at 600 and ^{13}C at 150 MHz) using solvent signals as reference; in $CDCl_3$ or (D_6)DMSO; chemical shifts (´) in ppm;

coupling constants *J* in Hz. The majority of the ^{13}C signals were assigned with the aid of DEPT spectra. HR-ESI-MS: *Bruker maXis* spectrometer.

2. *Starting Materials.* 3-Amino-5-arylpyrazoles **1a–d** were prepared starting with 3-aryl-3-oxopropanenitrile and $NH_2NH_2 \cdot H_2O$, based on known protocols [11]. Dialkyl dicyanofumarates **4a–c** were obtained from the corresponding alkyl cyanoacetates by reaction with $SOCl_2$ [12]. The $SOCl_2$ used for this reaction must be of 'gold labeled' quality or freshly purified by distillation over quinoline and linseed oil [13]. 1,2-Dichloroethane was used as commercially available and distilled over K_2CO_3 prior to the use. *N,N*-Dimethylformamide (DMF) was used as a commercial solvent without additional purification.

3. *Reactions of 3-Amino-5-arylpyrazoles* **1** *with Dialkyl Dicyanofumarates* **4**. Method *A*: A soln. of the corresponding 3-aminopyrazole **1** (1 mmol) and dialkyl dicyanofumarate **4** (1 mmol) in 1,2-dichloroethane (2 ml) was heated at reflux. The progress of the reaction was monitored by TLC, and in all cases complete conversion of **1** was evidenced after 2 h. Then, the solvent was evaporated and the obtained residue was triturated with a small amount of MeOH. After 1 h at r.t., the precipitated yellowish major product **10** was filtered and additionally purified by recrystallization from EtOH. The mother liquor collected after filtration of **10** was evaporated and separated by prep. TLC (silica gel, CH_2Cl_2/MeOH 99:1). After repeated development, the minor products **11** were isolated as a less polar fraction (R_f *ca*. 0.80), and a small amount of **10** was also separated as a more polar fraction (R_f *ca*. 0.15). Products **11** were purified by crystallization from MeOH/CH_2Cl_2 and the combined portions of **10** were obtained as analytically pure samples after recrystallization from alcoholic solutions.

Method *B*: A soln. containing corresponding 3-aminopyrazole **1** (1 mmol) and an equimolar amount of dialkyl dicyanofumarate **4** in DMF (2 ml) was placed in a

closed 25 ml round bottomed flask and kept at r.t. overnight. Then, H_2O (10 ml) was added and the formed suspension was magnetically stirred at r.t. for *ca*. 1 h. The precipitated yellowish solid was separated by filtration using a paper filter, dried, and additionally purified by recrystallization from an alcoholic solution. In this procedure, the mother liquor obtained after filtration of **10** was not analyzed and no additional work-up was carried out. In the ^{1}H-NMR spectra of the crude products **10**, trace amounts of products **11** were also observed. After recrystallization from an alcoholic solution, products **10** were obtained as analytically pure samples.

Method *C*: Analogous to method *B*, but the DMF-soln. was heated to 100° for 4 to 11 h.

*Methyl 3-Cyano-2,7-dihydro-5-(4-methylphenyl)-2-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10a**): Yield: 230 mg (75%; method *A*), and 278 mg (90%; method *B*). Yellow crystals. M.p. 308–312º (decomp., EtOH). IR (KBr): 3365–2926v*s* (br., NH), 2229*m* (CN), 1740*s* (C=O), 1659v*s* (br., C=O), 1608*m*, 1513*m*, 1466*m*, 1364*m*, 1252*s*, 1132*w*, 1012*w*, 823*m*, 674*m*, 559*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.37 (*s*, Me); 3.47 (*s*, MeO); 7.29, 7.36 (*AB*, J_{AB} = 7.9, 4 arom. H); 12.83, 14.11 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 21.2 (Me); 53.3 (MeO); 115.0 (CN); 128.5, 129.7 (4 arom. CH); 100.0, 125.1, 140.0, 141.6, 146.3, 150.2 (6 signals for 7 sp^2 C); 160.2 (br.), 163.7 (2 C=O). HR-ESI-MS: 331.08008 ([*M*+Na]$^+$, $C_{16}H_{12}N_4NaO_3$; calc. 331.08016).

*Dimethyl 4-Amino-7-(4-methylphenyl)pyrazolo[2,3-*a*]pyrimidine-2,3-dicarboxylate* (**11a**). Yield: 32 mg (10%; method ***A***). Colorless crystals. M.p. 258–260º (hexane/CH_2Cl_2). IR (KBr): 3415*s* (br., NH), 3314*s* (NH_2), 2951*w*, 1755*s* (C=O), 1684*s* (C=O), 1632*s* , 1611*m*, 1591*s*, 1570*m*, 1539*w*, 1453*m*, 1437*m*, 1326*s*, 1313*m*, 1241*s*, 1213*m*, 1092*w*, 1029*w*, 802*s*, 621*m*. ^{1}H-NMR ($CDCl_3$): 2.40 (*s*, Me); 3.89, 3.97 (2*s*, 2 MeO); 6.83 (*s*, H–C(8)); 7.18 (br. *s*, NH); 7.27, 7.85 (*AB*, J_{AB} = 8.0, 4 arom. H); 8.58

(br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 21.4 (Me); 52.3, 52.9 (2 MeO); 95.9 (C(8)-pyrazole); 126.6, 129.5 (4 arom. CH); 88.7, 129.1, 139.8, 147.9, 149.4, 152.4, 158.1 (7 signals for 7 sp^2 C); 165.9, 166.8 (2 C=O). HR-ESI-MS: 363.10674 ([*M*+Na]$^+$, $C_{17}H_{16}N_4NaO_4$; calc. 363.10638).

*Ethyl 3-Cyano-2,7-dihydro-5-(4-methylphenyl)-2-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10b**): Yield: 260 mg (81%; method *A*), and 295 mg (91%; method *B*). Yellowish powder. M.p. 290–294° (decomp., MeOH). IR (KBr): 3382–2803v*s* (br., NH), 2228*m* (CN), 1739*s* (C=O), 1663v*s* (br., C=O), 1617*m*, 1512*s*, 1467*s*, 1375*m*, 1352*w*, 1243v*s*, 1188*m*, 1018*m*, 823*m*, 719*w*, 683*w*, 557*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.89 (*t*, *J* = 7.2, *Me*CH$_2$); 2.37 (*s*, MeC$_{Ar}$); 3.95 (*q*, *J* = 7.2, MeC*H*$_2$); 7.18, 7.36 (*AB*, J_{AB} = 8.0, 4 arom. H); 12.82, 14.13 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 13.2 (*Me*CH$_2$); 21.1 (*Me*C$_{Ar}$); 63.0 (Me*C*H$_2$); 114.8 (CN); 128.4, 129.2 (4 arom. CH); 99.2, 124.9, 140.0, 141.3, 146.5, 150.4 (6 signals for 7 sp^2 C); 159.9 (br), 163.0 (2 C=O). HR-ESI-MS: 345.09599 ([*M*+Na]$^+$, $C_{17}H_{14}N_4NaO_3$; calc. 345.09581).

*Diethyl 4-Amino-7-(4-methylphenyl)pyrazolo[2,3-*a*]pyrimidine-2,3-dicarboxylate* (**11b**). Yield: 50 mg (13%) (method *A*). Colorless crystals. M.p. 218–220° (hexane/CH_2Cl_2). IR (KBr): 3382*s* (br., NH), 3287*s* (br., NH$_2$), 2987*w*, 2975*w*, 1741*s* (C=O), 1683*s* (C=O), 1635*s*, 1595*s*, 1569*m*, 1540*w*, 1453*w*, 1393*w*, 1318*s*, 1236v*s*, 1213*m*, 1087*m*, 1025*w*, 799*m*. ^{1}H-NMR ($CDCl_3$): 1.35, 1.43 (2*t*, *J* = 7.2, 2*Me*CH$_2$); 2.40 (*s*, MeC$_{Ar}$); 4.35, 4.43 (2*q*, *J* = 7.2, 2MeC*H*$_2$); 6.83 (*s*, H–C(8)); 7.19 (br. *s*, NH); 7.28, 7.86 (*AB*, J_{AB} = 8.1, 4 arom. H); 8.70 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 14.0, 14.1 (2 *Me*CH$_2$); 21.3 (*Me*C$_{Ar}$); 61.4, 62.1 (2 Me*C*H$_2$); 95.6 (C(8)); 126.5, 129.5 (4 arom. CH); 87.8, 129.1, 139.7, 147.9, 149.5, 152.6, 157.9 (7 signals for 7 sp^2 C); 165.7, 166.4 (2 C=O). HR-ESI-MS: 391.13812 ([*M*+Na]$^+$, $C_{19}H_{20}N_4NaO_4$; calc. 391.13768).

*Isopropyl 3-Cyano-2,7-dihydro-5-(4-methylphenyl)-2-oxo-1*H-*pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10c**): Yield: 222 mg (66%; method *A*), and 260 mg (77%; method *B*). Yellow powder. M.p. 254–257° (decomp., MeOH). IR (KBr): 3439–2750v*s* (br., NH), 2230*m* (CN), 1734*s* (C=O), 1661v*s* (br., C=O), 1620*m*, 1513*m*, 1466*m*, 1375*m*, 1249*s*, 1102*m*, 1006*m*, 847*w*, 823*m*, 683*w*, 557*w*. ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*d*, *J* = 6.6, *Me*$_2$CH); 2.37 (*s*, MeC$_{Ar}$); 4.80–4.82 (*m*, Me$_2$C*H*); 7.32–7.35 (*m*, 4 arom. H); 12.81, 14.12 (2 br. *s*, 2 NH). ^{13}C NMR ((D$_6$)DMSO): 20.8 (*Me*$_2$CH); 21.1 (*Me*C$_{Ar}$); 71.6 (Me$_2$*C*H); 114.8 (CN); 128.5, 129.5 (4 arom. CH); 99.3, 124.8, 140.1, 141.5, 146.9, 150.4 (6 signals for 7 sp^2 C); 160.0 (br.), 162.9 (2 C=O). HR-ESI-MS: 359.11123 ([*M*+Na]$^+$, C$_{18}$H$_{16}$N$_4$NaO$_3$; calc. 359.11146).

*Diisopropyl 4-Amino-7-(4-methylphenyl)pyrazolo[2,3-*a*]pyrimidine-2,3-dicarboxylate* (**11c**). Yield: 41 mg (10%; method *A*). Colorless crystals. M.p. 162–164° (hexane/CH$_2$Cl$_2$). IR (KBr): 3420*m* (br., NH), 3315*m* (br., NH$_2$), 2980*m*, 2934*w*, 1738*s* (C=O), 1677v*s* (C=O), 1614*m*, 1593v*s*, 1571*m*, 1455*m*, 1372*m*, 1334*m*, 1313*m*, 1244*s*, 1214*m*, 1166*m*, 1105*s*, 1019*m*, 798*m*. ^{1}H-NMR (CDCl$_3$): 1.36 (*d*, *J* = 6.0, *Me*$_2$CH); 1.44 (*d*, *J* = 6.6, *Me*$_2$CH); 2.40 (*s*, MeC$_{Ar}$); 5.23–5.28 (*m*, 2 Me$_2$C*H*); 6.84 (*s*, H–C(8)); 7.18 (br. *s*, NH); 7.28, 7.86 (*AB*, J_{AB} = 7.9, 4 arom. H); 8.71 (br. *s*, NH). ^{13}C-NMR (CDCl$_3$): 21.4 (*Me*C$_{Ar}$); 21.7, 21.8 (2 *Me*$_2$CH); 69.6, 70.0 (2 Me$_2$*C*H); 95.5 (C(8)); 126.5, 129.5 (4 arom. CH); 88.1, 129.2, 139.6, 147.9, 149.5, 152.9, 157.8 (7 signals for 7 sp^2 C); 165.3, 165.9 (2 C=O). HR-ESI-MS: 419.16950 ([*M*+Na]$^+$, C$_{21}$H$_{24}$N$_4$NaO$_4$, calc. 419.16898).

*Methyl 3-Cyano-2,7-dihydro-5-phenyl-2-oxo-1*H-*pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10d**): Yield: 157 mg (53%; method *A*), and 265 mg (90%; method *B*). Yellowish powder. M.p. 324–330° (decomp., MeOH). IR (KBr): 3367–2795v*s* (br., NH), 2226*m* (CN), 1746*s* (C=O), 1659v*s* (br., C=O), 1618*m*, 1545*m*, 1511*s*, 1466*s*, 1365*m*, 1247v*s*, 1138*w*, 1026*s*, 866*m*, 763*m*, 701*m,* 669*m*, 561*m*. ^{1}H-NMR

((D$_6$)DMSO): 3.42 (*s*, MeO); 7.35–7.45 (*m*, 2 arom. H); 7.50–7.60 (*m*, 3 arom. H); 12.82, 14.12 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 53.1 (MeO); 114.8 (CN); 128.5, 129.0, 129.9 (5 arom. CH); 100.2, 142.1, 145.8, 150.0 (4 signals for 6 sp^2 C); 160.2 (br.), 163.5 (2 C=O). HR-ESI-MS: 317.06468 ([*M*+Na]$^+$, $C_{15}H_{10}N_4NaO_3$, calc. 317.06451).

*Ethyl 3-Cyano-2,7-dihydro-5-phenyl-2-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10e**): Yield: 250 mg (81%; method *C*). Yellow crystals. M.p. 298–302º (decomp., EtOH). IR (KBr): 3390–2900v*s* (br., NH), 2231*m* (CN), 1740*s* (C=O), 1678v*s* (br., C=O), 1639*s*, 1565*m*, 1523*w*, 1450*m*, 1344*w*, 1238v*s*, 1177*m*, 1021*m*, 910*m*, 769*m*, 749*m*, 648*w*. ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*t*, *J* = 7.2, *Me*CH$_2$); 3.91 (*q*, *J* = 7.2, MeC*H*$_2$); 7.43–7.51 (*m*, 4 arom. H), 12.88, 14.13 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 13.1 (*Me*CH$_2$); 62.8 (Me*C*H$_2$); 114.7 (CN); 128.5, 128.9, 130.0 (5 arom. CH); 99.8, 141.1, 146.5, 150.1 (4 signals for 6 sp^2 C); 159.8, 163.1 (2 C=O). MS: 308 (100, M^+), 235 (27),149 (51), 77 (43). Anal. calc. for $C_{16}H_{12}N_4O_3$ (308.29): C 62.33, H 3.92, N 18.17; found: C 62.24, H 3.85, N 18.23.

*Isopropyl 3-Cyano-2,7-dihydro-5-phenyl-2-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10f**): Yield: 220 mg (68%) (method *C*). M.p. > 300º (decomp.). 3400–2900v*s* (br., NH), 2229*m* (CN), 1737*s* (C=O), 1678v*s* (br., C=O), 1639*s*, 1564*m*, 1508*m*, 1465*m*, 1374*w*, 1241v*s*, 1179*m*, 1102*m*, 1014*w*, 909*m*, 830*w*, 767*m*, 720*m*, 700*m*, 645*w*, 567*w*. ^{1}H-NMR ((D$_6$)DMSO): 0.99 (*d*, *J* = 6.6, *Me*$_2$CH); 4.79 (*m*, Me$_2$C*H*); 7.45–7.54 (*m*, 5 arom. H); 12.83, 14.14 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 20.8 (*Me*$_2$CH); 71.5 (Me$_2$*C*H); 114.7 (CN); 128.6, 128.9, 130.0 (5 arom. CH); 99.6, 141.5, 146.5, 150.1 (4 signals for 6 sp^2 C); 160.1 (br.), 162.8 (2 C=O). MS: 322 (58, M^+), 280 (100), 263 (17), 179 (17), 152 (19), 124 (15), 98 (23), 77 (55).

Anal. calc. for $C_{17}H_{14}N_4O_3$ (322.32): C 63.35, H 4.38, N 17.38; found: C 63.49, H 4.25, N 17.31.

*Methyl 3-Cyano-2,7-dihydro-5-(4-chlorophenyl)-2-oxo-1*H*-pyrazolo[3,4-b]pyridine-4-carboxylate* (**10g**): Yield: 260 mg (79%) (method *C*). M.p. 299-306º (decomp., MeOH). IR (KBr): 3450–2850v*s* (br., NH), 2229*m* (CN), 1737*s* (C=O), 1651v*s* (br., C=O), 1509*m*, 1364*m*, 1252*s*, 1092*m*, 1014*m*, 837*s*, 677*m*(br.) ^{1}H-NMR ((D$_6$)DMSO): 3.44 (*s*, MeO); 7.25, 7.30 (br.) (*AB*, J_{AB} = 7.9, 4 arom. H). MS: 328 (37, M^+), 139 (100), 111 (35), 75 (33.6). Anal. calc. for $C_{15}H_9ClN_4O_3$ (328.71): C 54.81, H 2.76, N 17.04; found: C 54.71, H 2.69, N 17.11.

*Ethyl 3-Cyano-2,7-dihydro-5-(4-chlorophenyl)-2-oxo-1*H*-pyrazolo[3,4-b]pyridine-4-carboxylate* (**10h**): Yield: 230 mg (67%) (method *C*). M.p. 283-287º (decomp., MeOH). IR (KBr): 3382–2800v*s* (br., NH), 2230*w* (CN), 1747*s* (C=O), 1659v*s* (br., C=O), 1467*s*, 1389*m*, 1253v*s*, 1092*m*, 1018*m*, 835*m*, 665*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.87 (*t*, *J* = 7.2, *Me*CH$_2$); 3.88 (*q*, *J* = 7.2, MeC*H*$_2$); 7.10, 7.28 (br.) (*AB*, J_{AB} = 8.0, 4 arom. H); 12.94, 14.16 (2 br. *s*, 2 NH). MS: 328 (M^+). Anal. calc. for $C_{16}H_{11}ClN_4O_3$ (342.74): C 56.07, H 3.23, N 16.35; found: C 56.07, H 3.23, N 16.35.

*Isopropyl 3-Cyano-2,7-dihydro-5-(4-chlorophenyl)-2-oxo-1*H*-pyrazolo[3,4-b]pyridine-4-carboxylate* (**10i**): Yield: 250 mg (70%) (method C). M.p. > 300º (decomp., MeOH). IR (KBr): 3420–2750v*s* (br., NH), 2229*w* (CN), 1728*s* (C=O), 1659v*s* (br., C=O), 1381*m*, 1255*m* (br.), 1095*m*, 1008*w*, 841*m*, 673*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.891.04 (*t*, *J* = 7.2, *Me*CH$_2$); 2.37 (*s*, MeC$_{Ar}$); 3.954.85 (*q*, *J* = 7.2,

MeCH_2); 7.18, 7.36 (br.) (*AB*, J_{AB} = 8.0, 4 arom. H). MS: 356 (M^+). Anal. calc. for $C_{17}H_{13}ClN_4O_3$ (356.76): C 57.23, H 3.67, N 15.70; found: C 57.35, H 3.75, N 15.62.

Methyl 3-Cyano-2,6-dihydro-5-(trifluoromethyl)phenyl-2-oxo-1H-pyrazolo[3,4-b]pyridine-4-carboxylate (**10k**): Yield: 140 mg (38%; method *A*). M.p. 271–280º (decomp., MeOH). IR (KBr): 3200–2750v*s* (br., NH), 2247*s* (CN), 1736*s* (C=O), 1656*s* (br., C=O), 1622*m*, 1607*s*, 1501*s*, 1464*m*, 1411*m*, 1362*w*, 1328*vs*, 1258v*s*, 1137*s* (br.), 1068*s*, 1006*m*, 850*m*, 730*w*, 686*m*, 604*w* (br.), 560*w*. ^{1}H-NMR ((D$_6$)DMSO): 3.46 (*s*, MeO); 7.64, 7.92 (*AB*, J_{AB} = 8.4, 4 arom. H); 12.80, 14.15 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 53.1 (MeO); 114.8 (CN); 125.8, 129.4 (4 arom. CH); 121.5, 126.9, 134.1, 142.0, 144.6, 149.9 (6 sp^2 C); 124.2 (*d*, $^1J_{C,F}$ = 270.8, CF_3); 129.8 (*d*, $^2J_{C,F}$ = 32.0, *C*–CF_3); 160.8, 163.5 (2 C=O). HR-ESI-MS: 385.0516 ([*M*+Na]$^+$, $C_{16}H_9F_3N_4NaO_3$; calc. 385.0524).

7. *X-Ray Crystal-Structure Determination of* **10b**, **10k**, and **11c** (*Table 2* and *Figs. 1* and *2*)[2]). The measurements of **10k** and **11c** were performed on an *Agilent Technologies SuperNova* area-detector diffractometer [14] using CuK_α radiation (λ 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler, whereas those of **10b** were performed on a *Nonius KappaCCD* area-detector diffractometer [15] using graphite-monochromated MoK_α radiation (λ 0.71073 Å). Data reduction was performed with *CrysAlisPro* [14] (**10k**, **11c**) and *HKL Denzo* and *Scalepack* [16] (**10b**), respectively. The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction using spherical harmonics

[2]) CCDC-913237–913239. contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

[14] was applied in the cases of **10k** and **11c**. Equivalent reflections were merged. The data collection and refinement parameters are given in *Table 2*, and views of the molecules are shown in *Figs. 1* and *2*. The structures were solved by direct methods using *SHELXS97* [17] (**10k** and **11c**) or SIR92 [18] (**10b**), which revealed the positions of most non-H-atoms. In the case of **10k**, the F-atoms of the CF_3 group are disordered over two orientations. Two sets of positions were defined for these F-atoms and the site occupation factor of the major orientation of the CF_3 group refined to 0.893(3). Similarity restraints were applied to the chemically equivalent C–F and F···F distances, while neighboring atoms within and between each conformation of the disordered CF_3 group were restrained to have similar atomic displacement parameters. In all cases, the non-H-atoms were refined anisotropically. The amine H-atoms of **10k** and **11c** were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in all structures were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent atom (1.5 U_{eq} for Me groups). The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. In the cases of **10b** and **11c**, a correction for secondary extinction was applied. Neutral atom scattering factors for non-H-atoms were taken from [19a], and the scattering factors for H-atoms were taken from [20]. Anomalous dispersion effects were included in F_c [21]; the values for f' and f'' were those of [19b]. The values of the mass attenuation coefficients are those of [19c]. All calculations were performed using the *SHELXL97* [17] program.

Table 2. *Crystallographic Data for Compounds* **10d**, **10k**, *and* **11c**

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Legends

Table 1. *Reactions of* **1** *with Dialkyl Dicyanofumarates* **4**

Table 2. *Crystallographic Data for Compounds* **10d**, **10k**, and **11c**

Fig. 1. *ORTEP-Plots* [9] *of the molecular structures of* a) **10d** *and* b) *one of the disoerdered conformations of* **10k** (CF_3 disorder; 50% probability ellipsoids; arbitrary numbering of the atoms)

Fig. 2. *ORTEP-Plot* [9] *of the molecular structure of* **11c** (50% probability ellipsoids; arbitrary numbering of the atoms)

Table 1. *Reactions of* **1** *with Dialkyl Dicyanofumarates* **4**

1 (Ar)	**4** (R)	Reaction conditions[a])	**10** (Yield [%])	**11** (Yield [%])
a (4-MeC_6H_4)	**a** (Me)	*A*; *B*	**a** (75; 90)	**a** (10; 0)
	b (Et)	*A*; *B*	**b** (81; 91)	**b** (13; 0)
	c (^{i}Pr)	*A*; *B*	**c** (66; 77)	**c** (10; 0)
b (Ph)	**a** (Me)	*A*; *B*	**d** (53; 90)	
	b (Et)	*C*	**e** (81)	
	c (^{i}Pr)	*C*	**f** (68)	
c (4-Cl-C_6H_4)	**a** (Me)	*C*	**g** (79)	
	b (Et)	*C*	**h** (67)	
	c (^{i}Pr)	*C*	**i** (70)	
d (4-$CF_3C_6H_4$)	**a** (Me)	*A*	**k** (38)	

[a]) Method *A*: Boiling $ClCH_2CH_2Cl$, 2 h; method *B*: DMF, r.t., 16 h; method *C*: DMF, 100°, 11 h

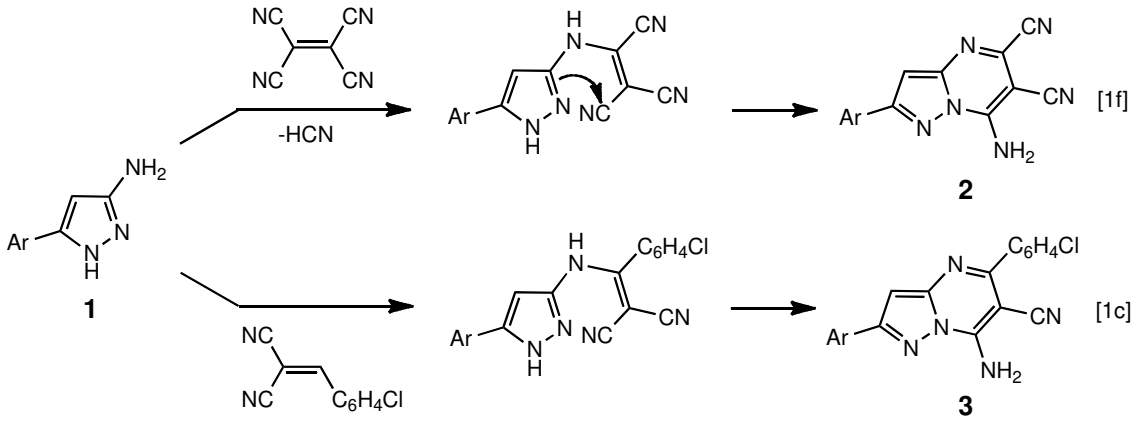
Table 2. *Crystallographic Data for Compounds* **10d**, **10k**, and **11c**

		10d	**10k**	**11c**
Crystallized from		MeOH	MeOH	Hexane/CH_2Cl_2
Empirical formula		$C_{15}H_{10}N_4O_3$	$C_{16}H_9F_3N_4O_3$	$C_{21}H_{24}N_4O_4$
Formula weight [g mol^{-1}]		294.27	362.27	396.44
Crystal color, habit		colorless, prism	yellow, prism	colorless, plate
Crystal dimensions [mm]		unknown	0.15 × 0.20 × 0.20	0.07 × 0.12 × 0.28
Temperature [K]		298(1)	160(1)	160(1)
Crystal system		monoclinic	monoclinic	triclinic
Space group		$P2_1/c$	$P2_1/c$	$P\bar{1}$,1
Z		4	4	2
Reflections for cell determination		2852	4986	26596
2θ range for cell determination [°]		5–55	6–142	6–149
Unit cell parameters	a [Å]	12.6815(4)	11.1763(4)	8.47828(19)
	b [Å]	8.7276(4)	9.8855(2)	9.5942(2)
	c [Å]	13.5654(6)	15.2144(6)	14.1580(3)
	α [°]	90	90	96.3610(17)
	β [°]	115.463(4)	111.113(4)	100.4022(17)
	γ [°]	90	90	115.294(2)
	V [$Å^3$]	1355.6(1)	1568.10(9)	1000.99(4)
D_X [g cm^{-3}]		1.442	1.534	1.315
Radiation		MoK_α	CuK_α	CuK_α
μ [mm^{-1}]		0.1046	1.160	0.762

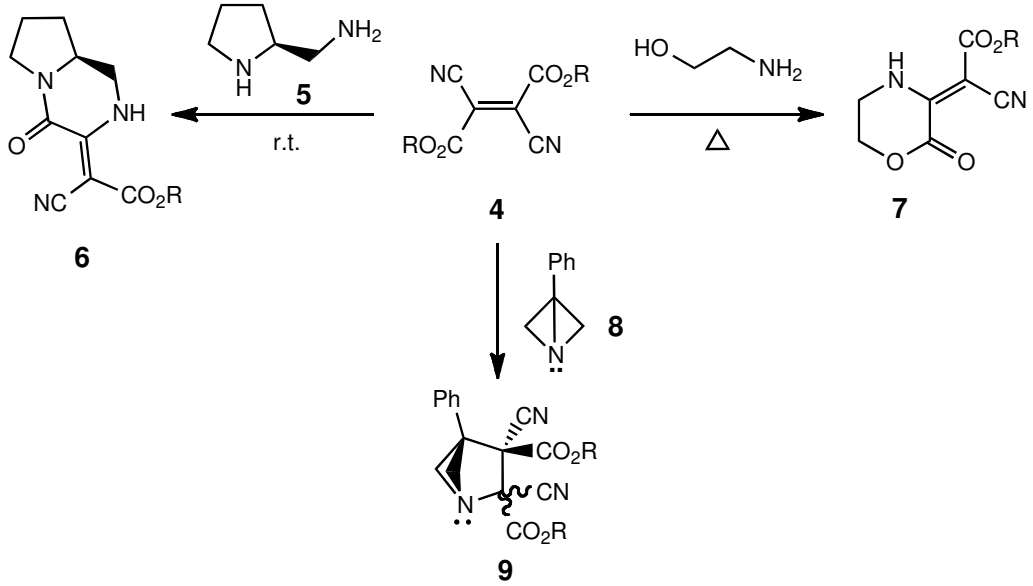
Scan type	ω	ω	ω
$2\theta_{(max)}$ [°]	55	142.2	148.8
Transmission factors (min; max)	-	0.464; 1.000	0.033; 1.000
Total reflections measured	5409	13798	37503
Symmetry independent reflections	3047	2966	4038
Reflections with $I > 2\sigma(I)$	1187	2443	3739
Reflections used in refinement	3047	2966	4038
Parameters refined; restraints	201; 0	272; 66	276; 0
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0566	0.0570	0.0364
$wR(F^2)$ (all data)	0.1211	0.1625	0.1022
Weighting parameters [a; b][a])	0.0416; 0	0.0750; 1.7522	0.0525; 0.2666
Goodness of fit	0.915	1.055	1.052
Secondary extinction coefficient	0.028(4)	-	0.0159(9)
Final Δ_{max}/σ	0.001	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.16; –0.17	0.40; –0.48	0.28; –0.19

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$

Scheme 1



Scheme 2



Scheme 3

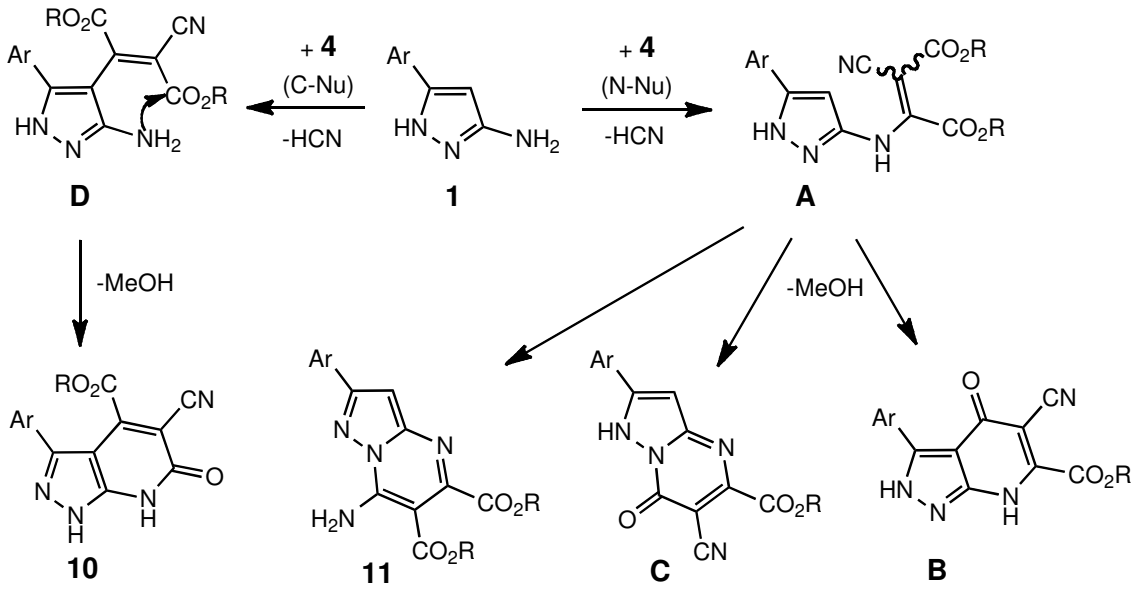
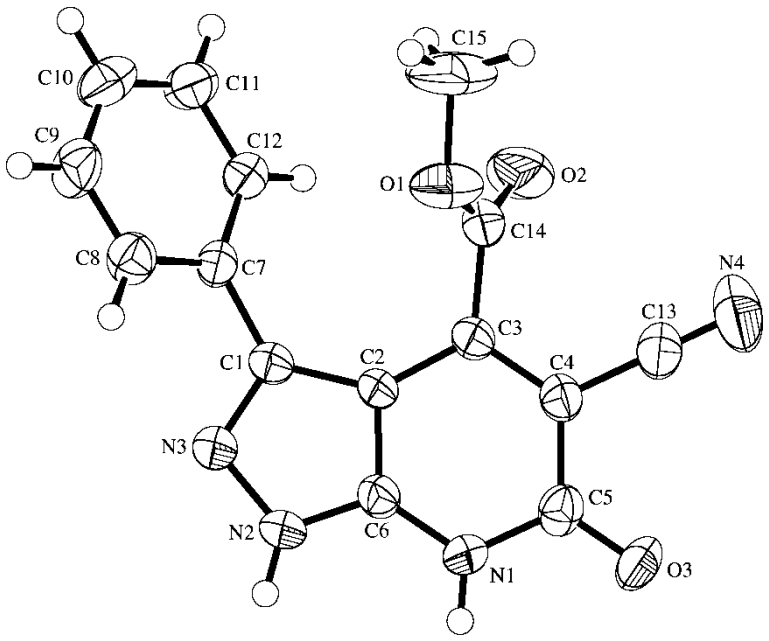

RO2C
CN
Ar
CO2R
HN
N
NH2
D
+ 4
(C-Nu)
-HCN
1
+ 4
(N-Nu)
-HCN
NC
CO2R
N
H
A
-MeOH
10
11
C
B
O
H2N

Figure 1

a)


C15
C10
C11
C9
C12
O1
O2
C14
C8
C7
N4
C13
C3
C1
C2
C4
N3
C5
N2
C6
N1
O3

b)

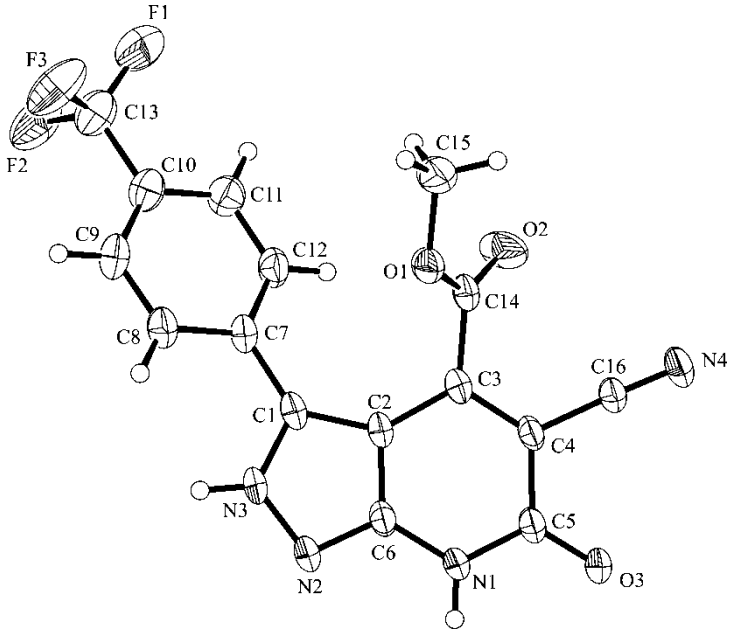
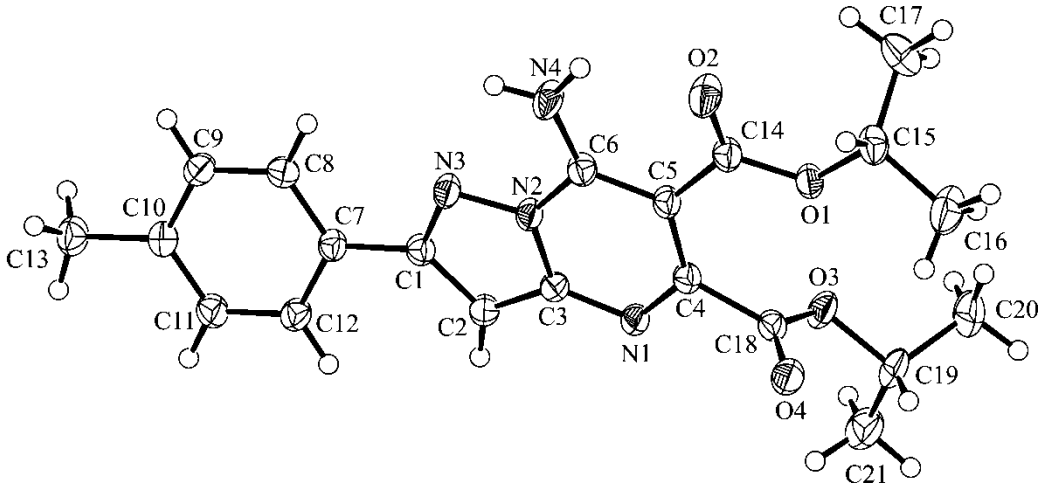

F1
F3
C13
F2
C10
C11
C9
C12
C15
O2
O1
C14
C8
C7
C16
N4
C3
C1
C2
C4
N3
C5
C6
O3
N2
N1

Figure 2


C17
N4
O2
C9
C8
N3
C6
C14
C15
C10
C7
N2
C5
O1
C16
C13
C1
O3
C11
C12
C2
C3
C4
C20
N1
C18
C19
O4
C21

Graphical Abstract